

In the Specification:

Please amend the specification as shown:

Please delete paragraph [0037] and replace it with the following paragraph:

[0037] The data suggest that attachment and spreading of cells are controlled by different mechanisms. A similar adhesion of cells to all collagen II variants indicates that the collagen II α chains of over 1000 amino acids each contain uniformly distributed sites for the attachment of chondrocytes. Since the adhesion of chondrocytes to the collagen II variants was reduced by anti $\beta 1$ integrin antibodies to about 15%, a value similar to that obtained with chondrocytes grown on bovine serum albumin coated plates, the main mechanism of the attachment involves $\beta 1$ integrins. It was postulated that the $\alpha 1\beta 1$, $\alpha 2\beta 1$ and $\alpha 10\beta 1$ integrins play a key role in the interaction of chondrocytes with collagen II ^{23, 41, 42}. However, the exact molecular mechanism of integrin mediated adhesion to collagen II is not known. Biochemical studies have shown that there is an important recognition site for the integrins in fibronectin ⁴³ and collagen VI ⁴⁴, a critical aspartate residue within a short peptide sequence (e.g. RGD, LDV). In collagen II, on the other hand, the role of such sequences in the interactions with integrins is not clear. As shown earlier ²⁷, the linear peptides containing RGD sequences were able to inhibit cell adhesion to denatured collagen II, but failed to compete with the native collagen for the integrin mediated binding of cells. However, the cyclic peptides with RGD sequences inhibit the binding of $\alpha 2\beta 1$ integrins to collagen ⁴⁵, which indicates that the stable conformation of the peptide is critical for the functioning of an integrin recognition site. It was also shown that chondrocytes are able to migrate toward tetra-RGD containing peptides ²². In human collagen II ⁴⁶, one RGD and two RGD sequences per one α chain are located in the D3 and D4 period, respectively (see Figure 9). Uniform binding of chondrocytes to all analyzed collagen II variants suggests, however, that the RGD-dependent mechanism is not significant for the $\beta 1$ integrin mediated adhesion of chondrocytes to collagen II. Recently, Knight *et al.* ²⁸ reported that in collagen I the GFPGER (**SEQ ID NO: 1**) sequence is as a critical recognition site for the $\alpha 1\beta 1$ and $\alpha 2\beta 1$ integrins. Still, platelets that bind to collagen III via $\alpha 2\beta 1$ integrins ^{47, 48} use a different mechanism of interaction, since collagen III does not contain a GFPGER (**SEQ ID NO: 1**) sequence ⁴⁹. Attachment of chondrocytes to collagen II with a deleted D3 period, the only region of human collagen II that contains the GFPGER (**SEQ ID NO: 1**) sequence, was not

different in comparison to other collagen II variants. Presumably, other amino acid sequences, randomly distributed through the collagen II molecule, are able to support $\beta 1$ mediated chondrocyte adhesion.

Please delete paragraph [0038] and replace it with the following paragraph:

[0038] Migration of chondrocytes depends on the interactions of integrins with components of the extracellular matrix ²². Clustering of integrins ^{50, 51} and the density of extracellular ligands ⁵² are important factors regulating cell migration. Data presented in this study demonstrate that collagen II supports the motility of chondrocytes. In the experiments with microtiter plates coated with different collagen II variants, chondrocytes were able to spread on full-length collagen II, and the collagen variants lacking the D1, D2 or D3 periods. However, the spreading was significantly altered when cells were cultured on the collagen II with deleted D4 period. The key role of the D4 period in the $\beta 1$ integrin mediated migration of chondrocytes was also demonstrated in the experiments with the three-dimensional matrices. We have demonstrated that chondrocytes are not able to migrate into nanofibrous scaffolds neither when the D4 period is deleted from collagen II monomer, nor when the $\beta 1$ integrin is selectively inactivated by antibodies. Our results do not provide an answer as to why the D4 period is critical for the chondrocyte spreading and migration on collagen II, and further studies will be required to find a minimal amino acid sequence of the D4 region that is critical for $\beta 1$ dependent cell motility. As previously indicated, the D4 period contains two out of three RGD sequences present in human collagen II, and such clustering of the RGD sequences is critical for the migration of cells. As recently shown by Maheshwari *et al.* ⁵³, the clustering of the YGRGD **(SEQ ID NO: 2)** peptide immobilized on a synthetic polymer was able to reduce the average ligand density required to support cell migration. The D-staggered axial alignment of collagen monomers, and the presence of RGD sequences in the narrow region of a molecule arranges these sequences into clusters that form a well-defined pattern (Fig. 9). Such a pattern makes the surface of collagen fibril competent for the integrin-mediated migration of cells.

Please delete the paragraph on page 21, lines 20-23 and replace it with the following paragraph:

28. Knight CG, Morton LF, Peachey AR, Tuckwell DS, Farndale RW, Barnes MJ. The collagen-binding A-domains of integrins alpha(1)beta(1) and alpha(2)beta(1) recognize the same specific amino acid sequence, GFOGER (SEQ ID NO: 3), in native (triple-helical) collagens. J Biol Chem 2000; 275:35-40.